

## IN THE SPECIFICATION

Please amend the specification as follows.

On page 1, line 5, please insert the following paragraph.

This application is a continuation of U.S. application serial number 10/018, 879, filed August 5, 2002, allowed, which is a 35 U.S.C. § 371 national phase application of international application serial no. PCT/US00/16879, filed June 19, 2000 and published in English on December 28, 2000, which is a continuation of, and claims priority to, U.S. application serial no. 09/336,548, filed June 19, 1999, the contents of each of which are incorporated by reference herein in their entireties.

On page 8, lines 1-3, please amend the text of the paragraph therein as follows.

(2) the activity of the therapeutic moiety is not eliminated once the lipophile has been severed by hydrolysis of the hydrolysable bond connecting the hydrophile and lipophile. Moreover, the ~~amphiphilicity~~amphiphilicity of the drug-oligomer conjugate may be adjusted as necessary to enable formulation of the drug in a lipophilic or hydrophilic carrier, or in an emulsion of microemulsion.

On page 15, line 10, please insert the following section.

### 3.2 Brief Description of the Drawings

Figure 1 illustrates a synthesis scheme for making drug-oligomer conjugates.

Figure 2 shows glucose response in dogs orally administered an OLE-insulin mixture at 1 mg/kg.

Figure 3 shows glucose response in dogs orally administered an OCT-insulin mixture at 1 mg/kg.

On page 22, lines 1-16, please amend the text of the paragraph therein as follows.

An alternative form of insulin suitable for use in the drug-oligomer conjugates of the present invention is insulin lispro, a newly developed analogue of human insulin in which the positions of the amino acids lysine and proline have been switched at the end of the  $\beta$  chain of the insulin molecule (Koivisto, V.A. "The human insulin analogue insulin lispro" Ann Med 1998 June 30:3 260-6). Insulin lispro with lysine at position B28 and proline at position B29 has a weaker tendency for self-association than human insulin. This leads to three major differences in pharmacokinetics: the action begins faster, has a higher peak and the duration is shorter than with human insulin. Thus, insulin lispro has a more precise action profile for the mealtime than human regular insulin. Insulin lispro is recommended to be injected within 15 min before the meal in contrast to 30-40 min for human insulin. Insulin lispro was designed to be used as a mealtime insulin. In another aspect, a ~~patient~~patient may be administered (either sequentially or simultaneously), a drug-oligomer conjugate comprising a fast-acting insulin (e.g., lispro) and a drug-oligomer conjugate having a slow acting insulin (e.g., ordinary insulin). In this way, a subject's glucose levels can be (1) quickly brought under control and (2) maintained for an extended period of time, an advantage that is not possible with a quick-acting insulin alone.

On page 40, line 20 through page 41, line 5, please amend the text of the paragraph therein as follows.

Throughout this specification reference has been made to various patent and non-patent references. The entire disclosure of each of these references is incorporated herein by reference,

as is the entire disclosure of each of the following references: U.S. Patent No. 5, 681,811 entitled "Conjugation-Stabilized Therapeutic Agent," issued October 28, 1997; U.S. Patent No. 5,438,040, entitled "Conjugation-Stabilized Polypeptide Compositions, Therapeutic Delivery and Diagnostic Formulations Comprising Same, and Method of Making and Using the Same," issued August 1, 1995; U.S. Patent No. 5, 359,030 entitled "Conjugation-Stabilized Polypeptide Compositions, Therapeutic Delivery and Diagnostic Formulations Comprising Same, and Method of Making and Using the Same," issued October 25, 1994; U.S. ~~Pat. Appl. No. 08/958,383~~ Patent No. 6,191,105, entitled "Hydrophilic and Lipophilic Balanced Microemulsion Formulations of Free-Form and/or Conjugation-Stabilized Therapeutic Agents such as Insulin," ~~filed October 27, 1997~~ issued February 20, 2001; U.S. Pat. Appl. No. 09/134,803, entitled "Blood-Brain Barrier Therapeutics,"; filed August 14, 1998; Chien, Y.W.; et al. ~~Drug Dev. Ind. Pharm.~~ *Drug Dev. Ind. Pharm.* 15:1601-1634 (1989); Radhakrishnan, B.; et al. ~~Proc. Intl. Symp. Control Rel. Bioactive Mater.~~ *Proc. Intl. Symp. Control Rel. Bioactive Mater.* 25:124-125 (1998); and Ekwuribe, N. AAPS Ann. Meeting Abst. S-102-S-103 (1998).